

IN THE UNITED STATES DISTRICT COURT
IN AND FOR THE EASTERN DISTRICT OF VIRGINIA
Alexandria Division

HALOZYME, INC.)	
11388 Sorrento Valley Road)	
San Diego, California 92121,)	
)	
Plaintiff,)	Civil Action No. _____
)	
v.)	
)	
MICHELLE K. LEE,)	
performing the functions and duties of Under)	
Secretary of Commerce for Intellectual Property)	
and Director of the United States Patent and)	
Trademark Office,)	
P.O. Box 1450, Alexandria, VA 22313-1450,)	
)	
Defendant.)	
)	

COMPLAINT

Plaintiff, Halozyyme, Inc. (“Plaintiff” or “Halozyyme”) brings this action to receive a patent against Defendant, MICHELLE K, LEE, Director, United States Patent and Trademark Office (“USPTO”), and alleges on knowledge, information and belief, as follows:

NATURE OF THE ACTION

1. This is an action brought pursuant to 35 U.S.C. § 145 by the assignee of U.S. Patent Application Serial No. 11/238,171 (“the ’171 Application”), Plaintiff Halozyyme, against the Acting Director of the USPTO seeking a judgment that Plaintiff is entitled to a patent for the invention specified in Claims 264-266, 278, 291-293, 295-298, 300, and 303 of the ’171 Application, which claims are the subject of a final decision by the Patent Trial and Appeal Board (“PTAB” or “Board”).

2. This civil action arises under 35 U.S.C. § 145 because Plaintiff Halozyne, to whom the applicants' rights in the '171 Application have been assigned, objects to the final decision of the PTAB in an appeal under 35 U.S.C. § 134(a) affirming the rejection of Claims 264-266, 278, 291-293, 295-298, 300, and 303 of the '171 Application.

THE PARTIES

3. Plaintiff Halozyne is a corporation organized under the laws of the State of California with its principal place of business at 11388 Sorrento Valley Road, San Diego, California 92121.

4. Defendant Michelle K. Lee (hereinafter the "Director") is the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office, acting in her official capacity.

JURISDICTION AND VENUE

5. This Court has jurisdiction and venue pursuant to 35 U.S.C. § 145.

6. This Complaint is being timely filed in accordance with 37 C.F.R. § 1.304(a)(1).

7. The PTAB Decision on Appeal (Appeal 2014-001770; Application 11/238,171) was mailed on July 27, 2016 (Exhibit 1), and the Request for Rehearing ("RFR Denial") (Exhibit 2) was denied and mailed on October 20, 2016. These decisions constitute a final decision under 37 C.F.R. § 41.2.

8. Plaintiff has not appealed the PTAB Decision on Appeal and the RFR Denial to the United States Court of Appeals for the Federal Circuit.

9. Plaintiff Halozyne has timely commenced this action within 63 days of the October 20, 2016, Decision on Request for Rehearing.

BACKGROUND

10. The invention described and claimed in the '171 Application generally relate to a specific pharmaceutical composition that comprises a glycosaminoglycanase recombinant protein known as "human-derived hyaluronidase" that contains three to six pendant moieties of polyethylene glycol (PEG) per hyaluronidase and that may be administered to a patient systemically. The claimed pharmaceutical composition would not have been obvious to an artisan of ordinary skill as of the '171 Application's priority date of February 23, 2005, contrary to the Board's Decision upholding the Examiner's finding of obviousness.

11. By way of background, a protein is a linear chain comprised of different amino acids that fold into a specific three-dimensional conformation. The specific three-dimensional conformation of a protein is necessary for it to achieve its function in the body. For example, if a protein is an enzyme that catalyzes a particular biological reaction, the specific three-dimensional conformation is required for that enzyme to exhibit its catalytic function. A "glycoprotein" is a protein that has undergone glycosylation and contains carbohydrate (glycan) groups attached to certain amino acid residues.

12. "Human hyaluronidase PH20," a human testicular hyaluronidase, is a large (in 60 kDa range) glycoprotein enzyme that the human body naturally produces, that comprises up to 509 amino acids. This 509 amino acid long glycoprotein includes 12 "cysteine" amino acids that specifically bond with each other to form six disulfide bonds crucial to maintaining the glycoprotein's specific three-dimensional conformation necessary for it to perform its enzymatic function.

13. "Human-derived hyaluronidase" is a human-engineered glycoprotein with the same, but truncated, amino acid sequence as human hyaluronidase PH20 (including the 12 "cysteine" amino acids that form the six disulfide bonds essential for enzymatic activity) that

produces a soluble version of PH20 while maintaining enzymatic activity. It is typically made using recombinant DNA methods in Chinese hamster ovary cells. Human derived-hyaluronidase enzyme acts (catalyzes) to degrade its substrate “hyaluronan,” a large, complex polysaccharide (also known as a glycosaminoglycan) in the body that exists ubiquitously in the extracellular matrix in a variety of cells, tissues and organs. Hyaluronan is associated with many tumor masses and acts as a shield, which restricts cancer-treating agents from efficiently entering the tumor and exerting their therapeutic effects.

14. As of 2005, Halozyme understood that human-derived hyaluronidase needed to be glycosylated in order to function as an enzyme in the body, but what specific role glycosylation played in the glycoprotein’s activity was unknown.

15. Clearance of recombinant human-derived hyaluronidase was not well understood at the time of the invention. It was believed that the large, recombinant “human-derived hyaluronidase” protein would not be cleared by the kidneys because its molecular mass was estimated to be between 60 and 64 kD (contrary to many smaller proteins PEGylated in the prior art), but rather, through the liver via the reticuloendothelial system (“RES”) and other pathways in the body. Because human-derived hyaluronidase is rapidly cleared from systemic circulation in minutes, it does not remain in the body long enough to reach tumor masses and effectively break up the large hyaluronan barriers.

16. Halozyme is a San Diego-based company dedicated to developing recombinant human-derived hyaluronidase to aid in drug delivery and treating cancers. Halozyme owns several U.S. and foreign patents related to the recombinant human-derived hyaluronidase glycoprotein.

17. In 2004-05, Halozyme employees and named inventors Louis Bookbinder, Anirban Kundu and Gregory Frost sought to devise a new form of human-derived hyaluronidase that would be soluble in the body at neutral pH, would circulate in the body longer and retain its enzymatic activity at neutral pH to break up hyaluronan, would be structurally stable so it would retain activity in the body, but would not remain too long in the body such that all hyaluronan in the body would be degraded.

18. The art provided no clear pathway to overcoming numerous impediments to maintaining both the specific activity (a measure of the catalytic activity of an enzyme normalized to the amount of protein) and selectivity of the new form of human-derived hyaluronidase in degrading hyaluronan. The art further provided no clear pathway to overcome other impediments necessary to this new form of human-derived hyaluronidase, such as (i) maintaining both solubility and activity at neutral pH so that the new form could circulate through the bloodstream, and (ii) increasing half-life to overcome RES clearance and interactions with potential inhibitors in the blood without creating toxicity in the body, so that the new form of human-derived hyaluronidase remains in the body long enough to circulate and reach tumor masses to effectively break up the large hyaluronan polysaccharides.

19. For example, PEGylation (the attachment of polyethylene glycol (PEG) moieties to a biologically relevant molecule, *e.g.*, protein) was just one of many potential pathways to modifying the human-derived hyaluronidase. And PEGylation for this purpose itself presented many more challenges relating to the size and branching of the PEG moiety, the chemistry of the PEG attachment, single versus multiple PEG attachments, and, perhaps most importantly, the effects of PEGylation on any specific protein.

20. Through extensive research, the three inventors ultimately conceived of, and reduced to practice, a pharmaceutical composition comprising human-derived hyaluronidase with three to six PEG moieties attached to the glycoprotein's molecule via its lysine residues (*i.e.*, 3-6 lysine's modified out of 31 total). This type of PEG-hyaluronidase conjugate remains soluble and enzymatically active at neutral pH, and is suitable for systemic administration into the body.

21. The results of that research are embodied in the '171 Application, titled "Soluble Glycosaminoglycanases and Methods of Preparing and Using Soluble Glycosaminoglycanases."

22. On August 20, 2012, Halozyme received a Final Rejection of all seventeen claims then pending in the '171 Application, and on December 20, 2012, filed a Notice of Appeal to the PTAB.

23. On July 27, 2016, the PTAB issued a Decision on Appeal (Exhibit 1) affirming the Final Rejection of all the claims then pending in the '171 Application.

24. On September 27, 2016, Halozyme requested a rehearing, and on October 20, 2016, the PTAB issued the Decision on Request for Rehearing (Exhibit 2) maintaining the affirmance of the Final Rejection.

25. Halozyme has accrued significant costs in attempting to obtain a patent based on the '171 Application.

COUNT UNDER 35 U.S.C. § 145

26. Plaintiff Halozyme repeats and re-alleges each and every allegation of paragraphs 1 through 25 above, and incorporates them by reference as if fully set forth herein.

27. The July 27, 2016, PTAB Decision on Appeal and the October 20, 2016, Decision on Request for Rehearing affirming rejections of all the claims then pending in the '171

Application was unwarranted by the facts, unsupported by substantial evidence, arbitrary, capricious, an abuse of discretion or otherwise not in accordance with law.

28. The Board affirmed the Examiner's obviousness rejection of the pending claims under 35 U.S.C. § 103(a) based on three prior art references: (a) Bookbinder *et al.*, WO 2004/078140, published Sept. 16, 2004 ("Bookbinder"); (b) Braxton, U.S. Patent No. 5,766,897, issued June 16, 1998 ("Braxton"); and (c) Thompson *et al.*, U.S. Patent No. 6,552,170, issued April 22, 2003 ("Thompson"). The Board further affirmed the grounds of non-statutory obviousness-type double patenting over U.S. Patent Nos. 7,767,429 (claims 9 and 10), 7,846,431 (claims 4 and 5), and 7,829,081 (claims 5 and 6) in view of Braxton and Thompson.

29. The evidence introduced in this matter will show that the Board fundamentally erred in affirming the rejections and that Plaintiff's pending patent application claims should have been allowed by the USPTO.

30. At its most basic level, the Board erred by failing to appreciate that an artisan of ordinary skill would understand that Braxton and Thompson teach PEG conjugation to cysteine residues with a preference for mono-PEGylation, which is inapplicable to the present invention of PEG-hyaluronidase compositions. An ordinary skilled artisan would not have been motivated by Braxton or Thompson to PEGylate the large hyaluronidase glycoprotein, (which acts on a gigantic-size substrate, hyaluronan), with three to six PEG moieties following the teachings of Braxton and/or Thompson. Specifically, the ordinary skilled artisan would have expected that the techniques disclosed were inapplicable, and in fact, most likely would destroy the requisite three-dimensional conformation of human-derived hyaluronidase, thereby rendering it inoperable.

31. Even if one were nevertheless to decide to PEGylate human-derived hyaluronidase, there is nothing in Braxton and Thompson that would have motivated the skilled artisan to look for, let alone find, a small range of three to six PEG moieties attached to the lysine residues of human-derived hyaluronidase.

32. The Board's treatment of the inventive contribution by the '171 Application as "routine optimization" is without evidentiary support.

33. Plaintiff Halozyne gives notice that it will seek to introduce additional evidence, not of record in the administrative proceeding at the USPTO, on the findings of fact, express conclusions in the Board's decision, and other issues pending before the Board for the Court's review, *de novo*, regarding the patentability of rejected Claims 264-266, 278, 291-293, 295-298, 300, and 303 in the '171 Application. This evidence will show:

- a. The scope and content of the prior art covered many different approaches for modifying a protein including, for example, super-sialation, dextran modification, and PEGylation. That scope and content further teaches that there is wide-variability in proteins and that there are circumstances where what is taught for modifying one protein may not be applicable to another protein;
- b. That one of ordinary skill in the art would understand that Braxton and Thompson do not teach hyaluronidase, PEGylating hyaluronidase, lysine PEGylation, or PEGylating hyaluronidase with three to six PEG moieties;
- c. That one of ordinary skill in the art would understand that the Bookbinder, Braxton and Thompson references do not teach each element of the rejected claims, and that to the artisan of ordinary skill, the Braxton and Thompson references teach away from the invention claimed;

- d. That one of ordinary skill in the art would not be motivated to combine the three references and would not have had a reasonable expectation of success in combining the reference teachings so as to achieve the invention as claimed, particularly since one of ordinary skill would understand that Braxton and Thompson teach PEG conjugation to cysteine residues with a preference for mono-PEGylation inapplicable to the human-derived hyaluronidase of the present invention;
- e. That one of ordinary skill in the art would understand that PEGylating recombinant human hyaluronidase PH20 with three to six PEG moieties for systemic administration (as well as further specific limitations within the claims) is hardly routine experimentation given specific issues of unpredictability related to activity, selectivity, solubility at neutral pH, increasing half-life to overcome premature RES-mediated clearance and interactions with inhibitors, changes in organ distribution that result from PEG modifications of PH20, chemistry of attachment of PEG, molecular weight of PEG attached, structure of the PEG attached, that the three cited references neither speak to the specific molecule claimed nor render predictably achieving it by actions that would be obvious to try in a finite and predictable manner;
- f. That secondary factors of nonobviousness, such as commercial success, long felt need, and unexpected results, further establish the nonobviousness of the invention claimed.

34. The PTAB Decision on Appeal (Exhibit 1) was further fundamentally flawed because it relied on factual findings that do not withstand scrutiny. Specifically:

- a. The Board's FF 1 that the "Bookbinder [Abstract] teaches that '[t]he invention relates to . . . soluble neutral active Hyaluronidase Glycoproteins (sHASEGP's)¹ . . . [and] sialated and pegylated forms of a recombinant sHASEGP to enhance stability and serum pharmacokinetics'" ignores that the quoted statement deletes the additional Abstract language that the improvements are "*over naturally occurring slaughterhouse (i.e., non-human) enzymes.*" Non-human (slaughterhouse) enzymes when used systemically may contain damaging contaminants and are more likely to trigger an immune response to the foreign protein – concerns not applicable to recombinantly produced, human-derived hyaluronidase for systemic administration.
- b. The Board's FF 2 finding that "Bookbinder [¶ 25] teaches '[m]odifications of sHASEGP to further prolong the half-life are provided. Chemical modifications of a sHASEGP with polymers such as polyethylene glycol . . . are provided'" fails to consider the requirements of the specific claims in the context of human-derived hyaluronidase, such as the uncertain impact of PEGylation on specific activity, selectivity, optimal pH, how to PEGylate the human-derived hyaluronidase specifically with three to six moieties or how to increase half-life and ensure proper *in vivo* (tumor) biodistribution for the specifically claimed molecules.
- c. The Board's FF 3 finding that "Bookbinder [¶ 49] teaches '[i]n some instances, sHASEGP's can be delivered systemically by intravenous infusion'" fails to appreciate that the recited paragraph does not refer to PEGylation as the means to

¹ Bookbinder also indicates that "human soluble PH-20 Hyaluronidase Glycoproteins" are included within sHASEGPs. (Bookbinder ¶ 18.)

achieve systemic delivery of human-derived hyaluronidase by intravenous administration. One of skill in the art would understand that Bookbinder ¶ 49 teaches away by expressly pointing to a much different solution than PEGylation, namely super-sialation, which had been taught in the art.

- d. The Board's FF 4 that "Bookbinder [¶ 372] teaches 'the sHASEGP polypeptides provided herein can be used . . . in combination with a second active compound, such as a therapeutically effective agent'" fails to appreciate that the cited paragraph does not refer or discuss PEGylated human-derived hyaluronidase, or its use in conjunction with a second active compound.
- e. The Board FF 5 that "Braxton teaches pegylation of proteins that are suitable for therapeutic uses" fails to appreciate that Braxton teaches site-specific introduction of cysteine followed by cysteine-directed PEGylation with a preference for mono-PEGylation, not PEG moieties conjugated to lysine residues in recombinant human-derived hyaluronidase. One of ordinary skill would understand that recombinant human-derived hyaluronidase is not a suitable candidate for cysteine-directed PEGylation and for mono-PEGylation. Braxton does not even list hyaluronidase or glycosaminoglycosidases among the extensive list of exemplary proteins or even exemplary classes of proteins suitable for cysteine-PEGylation. Also, Braxton highlights the uncertainties and drawbacks around random multi-PEGylation of lysine residues, and teaches against it.
- f. The Board's FF 6 that "Braxton teaches that '[t]he chemically modified proteins contain at least one PEG moiety, preferably at least two PEG moieties, up to a maximum number of PEG moieties bound to the protein without abolishing

activity The ratio of PEG to protein is preferably 1:1, more preferably 2:1, even more preferably 5:1, up to a 10:1 or 40:1 ratio of PEG molecules to protein” fails to appreciate that Braxton is directed to cysteine conjugation inapplicable to human-derived hyaluronidase, and that the ranges quoted are specifically limited in Braxton to cysteine conjugation.

- g. The Board’s FF 7 that “[a]n important teaching of [Thompson] is that pegylation decrease[s] the rate of clearance from [the] blood stream” fails to appreciate, *e.g.*, that Thompson addresses primarily (a) mono-PEGylation of two proteins to make a “dumbbell” conjugate, (b) cysteine conjugation inapplicable to human-derived hyaluronidase, and (c) kidney clearance that is not relevant to clearance of the human-derived hyaluronidase.

35. The Board’s decision upholding the Examiner’s rejections for obviousness-type double-patenting similarly erroneously relied on, and failed to properly consider, the foregoing teachings of Braxton and Thompson.

36. Halozyme is entitled to receive a Notice of Allowance from the USPTO confirming the patentability of Claims 264-266, 278, 291-293, 295-298, 300, and 303 of the ’171 Application.

PRAYER FOR RELIEF

WHEREFORE, Plaintiff Halozyme respectfully requests as follows:

1. Reversal of the July 27, 2016, PTAB Decision on Appeal and the October 20, 2016, Decision on Request for Rehearing by the PTAB at the USPTO;
2. A judgment that the ’171 Application is entitled to issuance of Letters Patent of the United States for the invention claimed in the claims of the ’171 Application denied by the PTAB decisions;

3. A decree pursuant to 35 U.S.C. § 145 authorizing the USPTO Director to issue a Notice of Allowance confirming the patentability of Claims 264-266, 278, 291-293, 295-298, 300, and 303 of the '171 Application; and,

4. For such other and further relief as the Court deems just and proper.

Dated: December 19, 2016

Respectfully submitted,

MCDERMOTT WILL & EMERY LLP

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